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REACTIVITY OF ORGANISM IN PROLONGED SPACE FLIGHTS

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16. Abstract

The paper presents an analysis of published data and the results of our own experiments which show that the state of weightlessness and hypodynamia result in a reduced orthostatic and vestibular resistance, increased sensitivity to infections, decreased endurance of accelerations and physical exercises and altered reactivity of the organism to drugs. These observations indicate the need for a comprehensive study of various consequences of weightlessness on the human body, especially weightlessness combined with other factors linked to long space flights.

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REACTIVITY OF ORGANISM IN PROLONGED SPACE FLIGHTS

by

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It has been established that weightlessness and hypodynamia produce certain changes in the functions of circulation, respiration, organs of excretion, analyzers and regulatory systems. It is natural that the noted functional reorganizations in the systems indicated above should inevitably lead to changes in the overall reactivity of the organism closely linked to its resistance.

The paper presents an analysis of published data and the results of our own experiments which show that the state of weightlessness and hypodynamia result in a reduced orthostatic and vestibular resistance, increased sensitivity to infections, decreased endurance of accelerations and physical exercises, and altered reactivity of the organism to drugs. These observations indicate the need for a comprehensive study of various consequences of weightlessness on the human body, especially weightlessness combined with other factors linked to long space flights.

As is known, long space flights will be accompanied by the effect on /107* human body of a whole set of factors in the period that the craft is put into orbit, noise, vibrations, accelerations, great neural-emotional stress, and during the orbital flight--dynamic weightlessness, hypodynamia of the altered gas medium, unusual periodicity of "day and night" shift, and so forth. Despite the slight pronouncement of the effects of each separately taken factor, their complex effect due to summation and accumulation can be very significant. Therefore the question of the effect of each factor separately and especially, their totality, on the human functional state

*Numbers in margin indicate pagination in original foreign text.

needs thorough investigation. The effect of weightlessness is the least studied.

The implemented orbital flights and materials obtained during simulation of the state of weightlessness by the method of prolonged hypodynamia under conditions of an immersion medium or by bed confinement show that in the human organism significant functional reorganizations of a number of organs and systems occur.

The works of many authors have firmly established that weightlessness and hypodynamia result in certain changes on the part of the indices of hemodynamics, respiration, organs of excretion, function of the analyzers, regulatory systems of the organism and different types of metabolism [10, 16, 18, 20, 24, 26, 27, 30, 32, 33, 34, 36, 37, 39, 42, 45, 46, 48]. It should be noted that the observed functional and biochemical disorders are accompanied in a number of cases by significant structural morphological changes. The depth of both the functional and morphological disorders in the conducted studies depended on the species and individual peculiarities of the organism, the nature of the model of the experiment, and its duration.

It is natural that the noted functional and morphological reorganizations in the systems indicated above should inevitably result in changes in the overall reactivity of the organism closely linked to its resistance. This is confirmed in the experiments to determine the orthostatic resistance, tolerance of accelerations, vestibular resistance, sensitivity to infections, drugs and other factors.

In fact a number of authors have convincingly demonstrated that in the cosmonauts after the end of flights [13, 9, 31, 35, 41], as well as in experiments simulating the state of weightlessness [28, 1, 15, 19, 44,47] with the conducting of an orthostatic test more pronounced changes are /108 observed on the part of the cardiovascular system (as compared to the initial data) which in a number of cases resulted in orthostatic collapse.

In our experiments [11], as well as in the studies of other authors [43] after lengthy (20-70-day) hypodynamia a decrease in the resistance to accelerations was noted on the average by 1.5-2 G. Under the influence of equivalent magnitudes of accelerations in the subjects a higher functional stress occurred in the main physiological systems of the organism. Thus, in the subjects with accelerations of 8-9 G the mean pulse rate after hypodynamia was 170±11 bt/min, while in the control rotations in the same subjects it was 149±13 bt/min. Analogous differences were also observed in the indices of external respiration.

In our studies (E. V. Lopayev) a decrease was noted in the threshold of resistance of the vestibular apparatus to linear accelerations and rolling for a long time after hypodynamia.

It is especially important to establish the fact of decrease in the immunobiological reactivity of man under conditions of prolonged hypodynamia. Kraus and Raab [40] and Lawton [42] and others have indicated that a strict bed confinement in a number of cases results in the emergence of serious complications in the form of pneumonia, exacerbation of cholelithiasis, thrombosis of veins and others. G. P. Mikhaylovskiy et al. [22, 23] noted in subjects in experiments with 62-day hypodynamia rhinopharyngitis, catarrh of the upper respiratory passages, and periodontitis. In our studies with 70-day hypodynamia complications were observed in the form of acute otitis, appendicitis, urethritis and pyodermia. These complications, undoubtedly, are a consequence of the decreased natural resistance of the body in its various links. In fact, the works of M. I. Kozar' [17] and G. P. Mikhaylovskiy et al. [22,23] convincingly demonstrated that during hypodynamia a suppression occurs in the phagocytic activity of the blood, decrease in the properdin level, depletion of the lysozyme activity of the saliva and gastric juice, and decrease in the bactericide function of the skin.

It goes without saying that the occurrence of morbid states during a flight, as well as the need in certain cases to increase the resistance of the organism of the cosmonaut to the extreme environmental factors

(ionizing radiation, hypoxia, accelerations, and others) can require the use of drugs. As is known, during the flight of the spacecraft "Apollo-7" W. Schirra, D. Eisele and W. Cunningham were forced to resort to taking drugs for therapeutic purposes.

At the same time it has been established that when prescribing drugs it is extremely important to consider the reactivity of the body, since the same chemical (pharmacological) substance taken in the same dose can under the same conditions (in one functional state of the organism) be of undoubted benefit, and in others--irreparable harm [2]. In fact, in the experiments on different types of animals it was established that after the effect of prolonged transverse-directed G-forces an increase is observed in the sensitivity to cardiac glucosides, narcotics and certain other preparations, and a decrease in the sensitivity to analeptics and analgesics; the body's reaction to the administration of mediators of the autonomic nervous system is altered [6,8]. Thus, for example, as is apparent from figure 1, the increase in motor activity of albino mice with the administration of phenamine after G-forces was less pronounced than in the control animals, which indicates the decrease in the specific effect of the preparation.

In our experiments data were also obtained that indicate the decrease in the analgesic effect of Promedol after the effect of transverse G-forces. Thus, in the experiments on rabbits it was established that an increase in the latent period of the motor reflex on the pain stimulant after administration of the preparation in the period of the aftereffect of the G-forces either was not noted or the deviations of this index were considerably less pronounced (fig. 2). The decrease in the pharmacological effect of Promedol under such conditions is also indicated by the experimental results from a study of the toxicity of the preparation. In fact, as is apparent from figure 3, the survival rate of animals from lethal doses of an analeptic after G-forces was greater than in the control.

Numerous studies have established that the reaction of a body damaged by ionizing radiation to drugs depends on the degree of severity of the sickness, its period of development, the dose and nature of the preparation

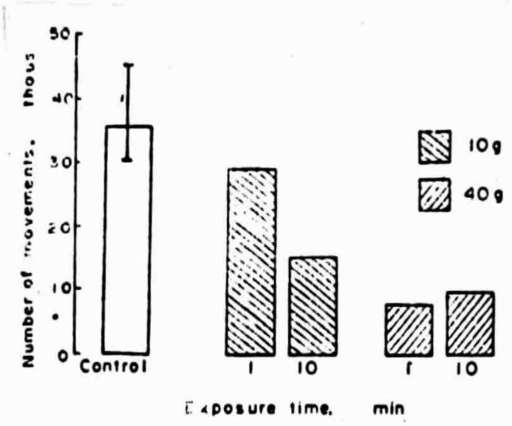

Figure 1. Effect of Transverse Accelerations on the Reactivity of White Mice to Benzedrine as Determined by the Number of their Movements for 120 min. (5 animals intraperioneally injected with the drug at a dose of 10 mg/kg). /109

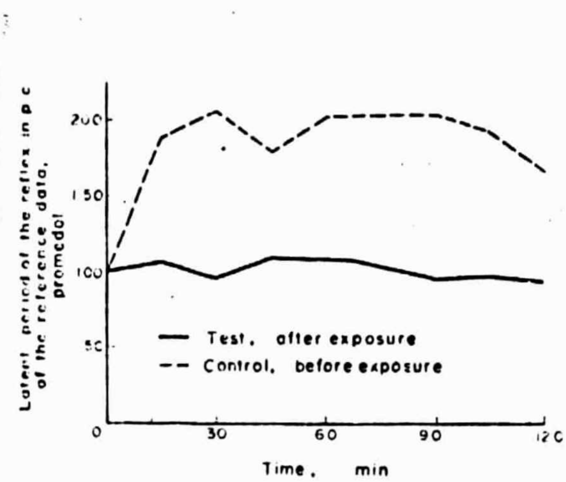

Figure 2. Change of the Latent Period of Flexor Reflex of Rabbits Subcutaneously Injected with Promedol at a Dose of 5 mg/kg before (dotted line) and after (solid line) Exposure to Accelerations. Mean Data in P.C. of the Referance Value.

[3,12]. Here in some cases an increase occurred, and in others--a decrease, and in third--distortion in the reaction to the administered substances.

The change in the composition of the surrounding gas medium (hypercapnia, hypoxia) also produces shifts in the reactivity of the body to

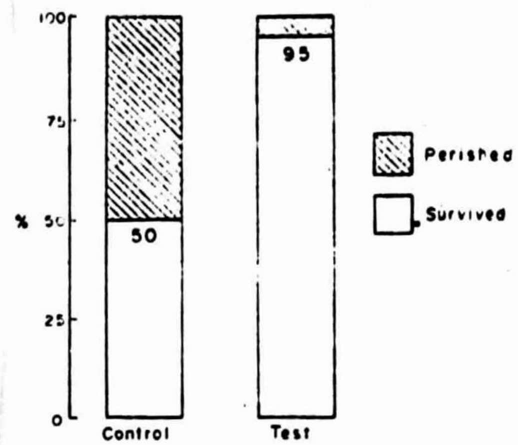

Figure 3. Effect of Transverse Accelerations (40 g for 10 min) on the Survival of White Mice from Intraperitoneal Injection of Toxic Doses of Promedol (130 mg/kg)

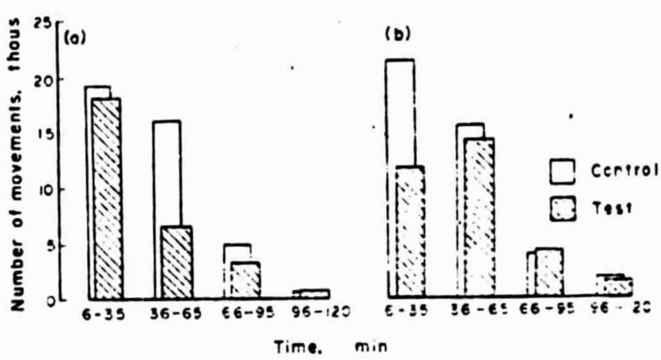

Figure 4. Effect of Hypercapnia on the Reactivity of White Mice to Benzedrine (Intraperitoneal Injections at a Dose of 10 mg/kg). The x-axis shows the number of movements in thousands and the y-axis shows the intervals of recordings after the injection in minutes.
A--the drug administered simultaneously with placement of the animals into a hypercapnic environment
B--the drug administered 30 min. after the enclosure of animals in the hypercapnic environment.

drugs [14, 29]. We established that in the gas medium with increased content of carbon dioxide (3-10%) the stimulating effect of the analeptics (caffeine and corasole) on the respiration of rabbits is significantly reduced or does not appear at all.

Under analogous conditions of the experiment the pharmacological effect of phenamine is reduced. This, in particular, is indicated by the results of an investigation of the motor activity of white mice with the administration of phenamine under normal conditions and in different periods of adaptation of the animals to the hypercapnic gas medium (fig. 4). Currently there are data obtained both in experiments on animals and in studies with people that show that the sensitivity of the organism after hypodynamia to drugs is also altered. Thus, L. A. Kravchuk and V. G. Ovechkin (1968) in conducting experiments on white mice established that after 37 days of /110 hypodynamia all the stages of narcosis with the use of barbamil are characterized by a number of peculiarities: the stage of excitation occurs more rapidly, complete falling asleep occurs later, and the duration of sleep is shorter. On the contrary, in our experiments made on albino rats hypokinesia lasting 14 and 28 days was accompanied by an increase in the depth and time of the intranarcotic narcosis (V. Ye. Belay, G. D. Glod) which, evidently, is due to the development in the brain of the processes of internal deceleration noted by R. Grandpierre (1968) also under conditions of real flight in weightlessness in monkeys.

With the use of strychnine, caffeine and phenamine in studies to simulate weightlessness in people a change was noted in the reaction of a number of main indices characterizing the function of the cardiovascular system (minimum, average, final systolic and pulse pressure, beat and per-minute volume of heart, rate of spread of pulse wave, etc.).

The findings do not make it possible to make any practical recommendations but they convincingly indicate the importance of conducting studies on the indicated questions.

Thus, even a brief survey of the problem, as it seems to us, indicates that weightlessness and hypodynamia which will be inevitable features of space flights in the near future, induce a whole gamut of functional, biochemical and morphological shifts in the organism resulting in a change in its overall reactivity. However, unfortunately, it is necessary to state that this problem until recently had not received the proper attention,

especially on the part of clinic physicians and pharmacologists responsible for certain areas of the medical support for prolonged space flights.

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Discussion

Grandpierre: It is particularly interesting to see that hypergravity and hypodynamia can modify, as it was shown in the past for hyperoxia and hypoxia, the activity of certain pharmacological drugs. Do you think that other environmental factors, encountered in aviation and in astronautics, can have the same effects?

Vasilyev: I am quite convinced that all environmental factors (temperature, vibration, radiations, noise), leading to substantial changes of the functional state of the organism, will also alter the reactivity to pharmacological agents.

Ingvar: You noted differences in drug effects in *hypercapnia*, immediately and after 30 minutes. Could these differences have been due to changes in the biocarbonate content of the brain tissue which would have changed the pH of the cerebro-spinal fluid? I think such factors must be considered before involving "inhibitory" systems as a cause of the altered drug effect.

Vasilyev: Your question undoubtedly deserves to be taken into serious consideration but I don't have any relevant experimental data which could serve as a basis for discussing these problems.

Gauer: I wonder whether you have tried vasopressin and whether you have seen any effect?

Vasilyev: I think that for the time being there is no theoretical basis for considering the possibility of preventing the hypodynamic syndrome with the aid of vasopressine and other similar preparations. These agents nevertheless could prove their usefulness in enhancing the tolerance of the organism to the increased gravitational force after prolonged flights in weightlessness. We do have data of this type and they have been partially reported by us in Madrid in 1966 and in New York in 1968.

Graybiel: I would like to hear Dr Vasilyev's opinion regarding the role of muscular work in causing the effects you have just described and those by Dr Gurovsky earlier in the day.

Vasilyev: My impression is that the role of hypodynamia in the pathogenesis of the observed effects is fundamental but not the only one.

Welch: In regard to the effect of hypoxia on drug effects, were you concerned with a change in O_2 only, or were the studies carried on at reduced pressure? Were the studies performed on animals acutely exposed, or were they acclimatised?

Vasilyev: There was no acclimatisation to hypoxia in our experiments; they were carried out under conditions of acute oxygen lack in the course of several hours. I think that the change in reactivity to drugs in those of our experiments you are mentioning, has not been due to decreased barometric pressure as such, but to hypoxia caused by the decreased oxygen tension in inspired air.

Andjus: My question will be similar to the one put by Prof. Ingvar. I would like to know what was actually the environment described as hypercapnic. Hypercapnia is a very potent hypothermia inducing agent in small laboratory animals such as mice. Have you observed any change in the body temperature of your animals? Hypothermia could, of course, participate in modifying the drug effects.

Vasilyev: I suppose that hypothermia can induce a marked change of the reactivity to pharmacological agents. I think, however, that under the conditions of our experiments, carried out in the majority of cases in the presence of 3 to 5 seldom 10% of CO_2 in the gas mixture, it is out of the question that hypothermia could be involved, especially if we take into consideration the specific ecological conditions under which mice live in their burrows where the concentration of CO_2 is always increased. However, I would not eliminate the possibility categorically and I would rather not enter a serious discussion with such a great specialist in the matter in question as Professor Andjus is, so much more because in our work we did not investigate mechanism responsible for the alteration of reactivity to pharmacological agents, but only described the fact itself.

Helvey: What type and number of subjects did you use in the 70-day hypodynamia experiments? Did you use bed rest or water immersion to simulate the hypodynamia of space flight?

Vasilyev: Investigations were carried out on young males, absolutely healthy and physically well fit. Each series included 6 persons. On the whole there were 22 men under investigation. Hypodynamia was induced by prolonged bed rest.